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A Clinically Prognostic Scoring System for Patients Receiving Highly Active Antiretroviral Therapy: Results from the EuroSIDA Study

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The risk of clinical progression for human immunodeficiency virus (HIV)–infected persons receiving treatment with highly active antiretroviral therapy (HAART) is poorly defined. From an inception cohort of 8457 HIV-infected persons, 2027 patients who started HAART during prospective follow-up were examined. Results were validated in another 2 groups of patients ($n = 1946$ and $n = 1442$). In total, 200 patients (9.9%) experienced clinical progression during 5177 person-years (incidence, 3.9/100 years). The most recently measured CD4 cell count, virus load, and hemoglobin level all were independently related to the risk of clinical progression, as was a diagnosis of severe AIDS before the start of HAART. On the basis of these findings, a scoring system was derived (range, 0–17). A single unit increase in the score was associated with a 38% increased risk of clinical progression (relative hazard, 1.38; 95% confidence interval, 1.33–1.43; $P < .0001$). The scoring system was validated with remarkably good agreement in the 2 other cohorts. This system can be used in patient and resource management.

The mortality and morbidity of human immunodeficiency virus (HIV)–infected persons has improved dramatically in recent years as a consequence of the widespread use of combination antiretroviral therapy—frequently termed highly active antiretroviral therapy (HAART) [1–4]. With HAART, the risk of death is estimated to be >85% lower than in the period before HAART [1], although the incidence remains at 2–4 cases per 100 person-years of follow-up (PYFU) and, thus, is substantially higher than for age-matched noninfected persons [1]. The suggested therapeutic goal of HAART is to completely inhibit viral replication and, hence, to eliminate the risk of developing resistance [5]. Randomized trials assessing the efficacy of antiretroviral drug combinations as part of HAART are using the HIV load in plasma as a primary end point [6–9]. Furthermore, changes in virus load during the course of therapy are now seen as the key parameter for evaluating the response to HAART and for determining the need for change of therapy [5]. Although changes in virus load are clearly associated with the subsequent clinical response in patients receiving HAART [10–15], the roles of other laboratory markers, such as CD4 cell count and hemoglobin levels, have been investigated less frequently.

Before the HAART era, several scoring systems were developed primarily to determine prognostic factors for survival after the first AIDS diagnosis [16–19]. Clinical and laboratory markers or a combination were used to derive such systems. More recently, most analyses demonstrating an association between virus load and clinical progression also used fixed values of virus load at some arbitrary baseline [10, 11, 13, 15]. However, because HAART can reverse many of the pathologic processes induced by HIV [20–22], the most recently measured laboratory values should be used to determine prognosis. A scoring system that uses surrogate markers that predict the clinical prognosis of patients on HAART would be useful in ongoing and future randomized trials and as part of the prognostic evaluation and management of individual patients. The aims of the present study were to develop a scoring system that takes into account the

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changes over time in the prognosis of individual patients in a large cohort of prospectively followed patients who started HAART and to validate the findings in other patient cohorts.

Patients and Methods

Patients. The EuroSIDA study is a prospective European study of 8457 HIV-infected patients from 4 cohorts from 60 centers in Europe and Israel. Study details have been published elsewhere [23]. Patients were ⩾16 years old at enrollment. Information was collected from patient case notes onto a standardized data collection form at baseline and every 6 months thereafter (a 6-month calendar period is defined as 1 follow-up). At each follow-up, CD4 cell counts and virus loads are measured. For each patient, the date of starting and stopping each antiretroviral drug is recorded, as is the use of drugs for prophylaxis against opportunistic infections. Dates of diagnosis of all AIDS-defining diseases are also recorded according to the 1993 Centers for Disease Control and Prevention clinical definition of AIDS [24]. Members of the coordinating office visit all centers periodically to ensure correct patient selection and accurate data collection. Follow-up is to February 2001. We have information available from up to 13 follow-up forms from cohort I (identified in 1994), up to 10 follow-up forms for cohort II (identified in 1995–1996), 7 follow-up forms for cohort III (identified in 1997), and 2 follow-up forms for cohort IV (identified in 1999).

The score was derived from a cohort of EuroSIDA study patients. The requirements for inclusion in the derivation cohort were defined so that the impact of the whole course of HAART could be evaluated. Patients had to have started a protease inhibitor (PI) or non-nucleoside reverse-transcriptase inhibitor (NNRTI) for the first time during prospective follow-up in the EuroSIDA study, the PI/NNRTI had to be a part of a HAART antiretroviral regimen (i.e., ⩾3 antiretroviral drugs in total), and patients had to have CD4 cell counts and virus loads measured during the 6 months before starting HAART (median time before HAART, 1 month for both CD4 cell count and virus load) and ⩾1 measurement of both markers after starting HAART. In all, 2027 people fulfilled the eligibility criteria.

The scoring system was validated on 2 different data sets, to ascertain how well the score predicted clinical progression among other patient groups (validation cohorts). The first validation was done for 1946 patients from the EuroSIDA cohort who started HAART before recruitment to the EuroSIDA study. The second validation was done for a cohort of 1442 patients from a single clinic in Barcelona, all of whom started HAART. These patients were identified from a clinical database in use at the hospital in which all HIV-related information is prospectively collected [25]. The cohort was initiated in 1985 and has enrolled 4291 patients. With regular intervals, the cohort is validated by crossing the patients with regional and national registries that detail mortality status and the occurrence of new AIDS-defining events.

Methods. Patient characteristics were compared by using χ^2 tests for categorical variables and nonparametric Wilcoxon and Kruskal-Wallis methods for continuous variables. Patient follow-up began at the start date of HAART (or, for the EuroSIDA validation cohort, at the time of enrollment in EuroSIDA) and ended at the first clinical progression (i.e., diagnosis of a new AIDS-defining event or death) or was censored at the last clinical follow-up for patients who did not progress.

Cox proportional hazards models were used to determine the factors associated with clinical progression. Initially, CD4 cell count, virus load, hemoglobin level, and weight were included in a Cox proportional hazards model as continuous time-updated variables. Clinical status also was included as a fixed categorical variable at start of HAART; the categories used were no AIDS, AIDS within the past 12 months of start of HAART (all diagnoses except progressive multifocal leukoencephalopathy [PML] and non-Hodgkin lymphoma [NHL]), and severe AIDS (PML and NHL). This stratification was decided on before commencing the analysis and was based on previous reports [17, 26]. CD4 cell count and virus load were initially log-transformed to obtain the best fitting model. Weight fitted as a time-updated continuous variable was not independently prognostic and was removed from this first model.

As the next stage, other variables were added to this basic model to see whether they provided additional prognostic information. Demographic variables included region of Europe, sex, risk group, race, age, and calendar quartile of the start of HAART. Treatment variables included whether the patient was treatment naive at start of HAART, time receiving nucleoside therapy before starting HAART, the number of new nucleosides added, and whether the regimen included a PI. Other variables included CD4 cell count nadir, maximum virus load before starting HAART, baseline values of weight, hemoglobin level, virus load, CD4 cell count, and changes in these variables from baseline (as time-dependent covariates). The use of disease-specific prophylaxis for opportunistic infections was considered to see whether results differed if patients not receiving prophylaxis when the CD4 cell count was low were excluded.

A final Cox model was constructed by using CD4 cell count, virus load, and hemoglobin level, which were modeled as time-dependent categorical variables. Categories of hemoglobin level and anemia were derived from EuroSIDA study data published elsewhere [27]. Normal hemoglobin level was defined as >14 g/dL for men and 12 g/dL for women, mild anemia was defined as 8–14 g/dL for men and 8–12 g/dL for women, and severe anemia was defined as <8 g/dL for both men and women. Commonly reported cutoffs of 50 cells/mm^3 and 200 cells/mm^3 for CD4 cell count and 500 and 10,000 HIV RNA copies/mL for virus load were applied (and were decided on before commencing the analysis). The natural logarithms of the relative hazards (RHs), with rounding, were used to derive a patient's score, which increased or decreased as new laboratory values became available. The incidence of clinical disease progression was calculated for each score and also was modeled in a Cox proportional hazards model as a time-dependent covariate to derive the RH associated with a 1 point increase in the score. The scoring system was validated on 2 validation cohorts. All analyses were made with SAS software (version 6.12; SAS Institute).

Results

Table 1 describes the 2027 patients who satisfied the inclusion criteria in the derivation cohort. The median age was 37 years. Medians of other values at the start of HAART were as follows: CD4 cell count, 244 cells/mm^3 (interquartile range [IQR], 134–

Table 1. Characteristics of 2027 patients starting highly active antiretroviral therapy (HAART).

Characteristic	No. (%) of subjects	CD4 cell counts at HAART, cells/mm^3		Log_{10} virus load at HAART, HIV RNA copies/mL		ARV naive		⩾3 New ARVs		PI HAART	
		Median	*P*	Median	*P*	%	*P*	%	*P*	%	*P*
Sex											
Male	1548 (76)	244	.16	4.3	<.001	21	.08	43	.15	86	.47
Female	479 (24)	246		4.0		17		39		87	
Risk											
Homosexual	880 (43)	261	.002	4.3	.002	22	.06	44	.6	84	.08
IDU	511 (25)	209		4.3		18		41		87	
Heterosexual	510 (25)	249		4.3		18		42		89	
Other	126 (6)	227		4.1		16		38		83	
Race											
White	1771 (87)	243	.6	4.30	.8	19	<.001	47	.08	86	.36
Other	256 (13)	250		4.30		29		42		84	
Region of Europe											
Southern	679 (34)	272	<.001	4.2	<.001	15	<.001	37	<.001	89	.002
Central	562 (28)	252		4.2		14		34		85	
Northern	757 (37)	215		4.5		27		52		84	
Eastern	29 (1)	280		4.4		62		79		69	
Cohort											
I	639 (32)	235	<.001	4.3	.43	11	<.001	33	<.001	87	.001
II	481 (24)	209		4.3		10		32		93	
III	828 (41)	260		4.3		28		51		83	
IV	79 (4)	319		4.4		70		84		70	
AIDS at HAART											
No	1577 (78)	263	<.001	4.2	<.001	21	.05	44	.009	85	.07
Yes	450 (22)	136		4.6		17		37		88	
Date started HAART, month/year											
Before 1/97	272 (13)	118	<0.001	4.6	<0.001	7	<0.001	16	<0.001	99	<0.001
1/97–1/98	986 (49)	241		4.4		21		41		96	
1/98–1/99	434 (21)	289		3.9		16		46		75	
1/99–1/00	252 (12)	291		4.2		35		63		63	
After 1/00	83 (4)	280		4.2		22		65		51	
Total	2027 (100)	244		4.3		20		42.0		86	

NOTE. Kruskal-Wallis (for >2 groups) test and Wilcoxon (2 groups) tests were used to compare groups. ARV, antiretroviral agent; HIV, human immunodeficiency virus; IDU, injection drug user; PI, protease inhibitor.

357 cells/mm^3); virus load, 4.3 log HIV RNA copies/mL (IQR, 3.5–4.9 log HIV RNA copies/mL); length of follow-up, 33 months (IQR, 20–41 months); and calendar time at the initiation of HAART, August 1997 (IQR, March 1997–June 1998). The patients were heterogeneous, and there were differences between demographic groups in terms of CD4 cell count and virus load at the start of HAART and in the proportions of patients who were antiretroviral naive at the start of HAART, those who started HAART with ⩾3 new antiretrovirals to which they were previously naive, and those who used a PI-based HAART rather than an NNRTI-based HAART. In all, 450 (22%) had a history of ⩾1 AIDS-defining event: the most common were *Pneumocystis carinii* pneumonia (110 [24%]), esophageal candidiasis (104 [23%]), and Kaposi's sarcoma (74 [16%]).

At the time of the analysis cutoff date (February 2001), 200 patients (9.9%) had experienced clinical events since the initiation of HAART (i.e., they had progressed). Of these, 59 (30%) died, 94 (47%) had a first AIDS-defining illness, and 47 (24%) who had ⩾1 AIDS-defining event before starting HAART progressed to a new AIDS-defining event. By 12 months after the start of HAART, 5.1% of patients (95% confidence interval [CI], 4.1%–6.1%) are estimated to have progressed to a new AIDS-defining event or died, 8.1% (95% CI, 6.8%–9.4%) had done so by 24 months, and 11.6% (95% CI, 10.0%–13.2%) had done so by 36 months. The most common AIDS-defining events that defined clinical progression were NHL ($n = 26$), esophageal candida ($n = 21$), pulmonary tuberculosis ($n = 14$), Kaposi's sarcoma ($n = 11$), HIV wasting syndrome ($n = 9$), and *P. carinii* pneumonia ($n = 7$). Among the patients who died, the cause of death was unknown for 23, an opportunistic infection for 1, Kaposi's sarcoma for 1, lymphoma for 3, AIDS dementia for 1, wasting for 3, bacterial infections for 5, suicide for 1, and 21 other causes, including myocardial infarctions, anemia, cancers, and liver-related deaths. For all the fatal cases associated with AIDS-defining events, the events were initially diagnosed before the start of HAART.

Over the median 33 months of follow-up, CD4 cell counts were measured a median of 11 times (IQR, 7–15 times), with a median frequency of 1 time per 2.7 months (22,574 measures in total). Virus load was measured a median of 10 times (IQR, 6–14 times; median frequency, 1 time per 2.9 months [21,780 measures in total]). Hemoglobin level was measured a median of 6 times (IQR, 4–8 times; 1 time per 5.2 months [11,497 measures in all]). For those with a clinical event during follow-up, the median lag time from the last CD4 cell count to the event was 2 months (IQR, 1–4 months). For virus load, the corresponding median value was also 2 months (IQR, 1–4 months), and for hemoglobin level it was 4 months (IQR, 2–7 months).

Of the factors assessed, 4 satisfied the requirement of being independently associated with the risk of clinical progression (see Patients and Methods): the most recently measurement of CD4 cell count, virus load, and hemoglobin level and the clinical status at the start of HAART. Table 2 shows the estimates of the association between each of these variables and the RH of clinical progression. Of note, the category of severe AIDS-defining illnesses was associated with an RH of 2.14 (95% CI, 1.05–4.36; $P = .036$) in the initial Cox model, in which variables were selected for inclusion in the score system (that model differed slightly from the model shown in table 2, because laboratory variables were included as continuous variables, not categories). Three equally sized groups of each laboratory marker were created by use of all markers measured during follow-up. Comparison of the highest third to the lowest third for each laboratory marker revealed that CD4 cell count was the strongest prognostic marker (RH, 4.52), followed by hemoglobin level (RH, 3.31) and virus load (RH, 1.88). From this and the results shown in table 2, it can be seen that the latest virus load added relatively little, although statistically significant, extra prognostic value.

We also investigated how these values changed when, instead of using the current marker values, those obtained 3, 6, 9, or 12 months previously were used. The RHs for CD4 cell count were 4.66, 4.37, 3.46, and 3.11, respectively; for hemoglobin level, the corresponding values were 3.24, 2.33, 2.04, and 1.53; and for virus load, the corresponding values were 1.89, 1.79, 2.25, and 2.20.

Scoring system. The RHs in table 2, based on the current marker values, were used to derive a simple score by multiplying the logarithms (base e) of the RHs in table 2 by 3 (thus, the value for the lowest score component is 1—the choice of this multiplying factor does not influence the predictive value of the score) and rounding to the nearest whole number. By our method, CD4 cell counts >200, 51–200, and ≤50 cells/mm^3 were scored as 0, 3, and 7, respectively; virus loads of <500, 500–999, and ≥1000 HIV RNA copies/mL were scored as 0, 1, and 2, respectively; hemoglobin levels that were normal or represented mild or severe anemia were scored as 0, 2, and 6, respectively; no previous severe AIDS diagnosis was scored as 0; and severe AIDS ever (NHL/PML) was scored as 2. By this method, a male patient receiving HAART with a CD4 cell count of 100 cells/mm^3, a virus load of 7000 HIV RNA copies/mL, and a hemoglobin level of 10 mg/dL (i.e., mild anemia) who had Kaposi's sarcoma diagnosed 18 months before starting HAART would have a score of 6: 3 (CD4 cells) + 1 (virus load) + 2 (mild anemia) + 0 (no previous severe AIDS diagnosis) = 6.

Risk of clinical disease by score: derivation cohort. The median score at the start of HAART was 2 (IQR, 0–5); only 1% of patients had a score ≥9 at the start of HAART (table 3). The overall incidence of clinical disease was 3.9/100 person-years. Table 4 shows the incidence of clinical progression for each value of the score; scores ≥12 were combined because of limited PYFU. A patient's score could increase or decrease as new laboratory marker values became available. In a Cox model in which the score was fitted as a continuous covariate, there was, on average, a 38% (95% CI, 33%–43%) higher risk of disease per 1 unit of higher score. This indicates that the latest value of the score strongly predicts the risk of clinical disease over the next few months (i.e., the typical between visit interval). We also evaluated the ability of the score to discriminate risk of clinical disease over a longer period (12 months) by defining a patient's current clinical status as the one noted 12 months earlier. As would be expected, the score was less discriminatory (RH/1 unit, 1.29; $P < .0001$) but was still highly predictive of outcome.

We considered whether the predictive value of the score appeared to change over time by fitting an interaction term with

Table 2. Multivariate relative hazards (RHs) of clinical progression, by Cox proportioned hazards model.

Parameter	RH	95% CI	*P*
Latest CD4 cell count, cells/mm^3			
>200	1.0	—	—
51–200	2.6	1.8–3.6	<.0001
≤50	9.3	6.1–14.0	<.0001
Latest virus load, HIV RNA copies/mL			
<500	1.0	—	—
500–9,999	1.3	0.9–2.0	.14
≥10,000	1.8	1.3–2.5	.001
Hemoglobin level			
Normal	1.0	—	—
Mild anemia	2.2	1.6–2.9	<.0001
Severe anemia	7.1	2.5–20.1	.0002
Clinical status[a]			
No new AIDS diagnosis	1.0	—	—
AIDS in last 12 months (except NHL/PML)	0.9	0.5–1.4	.85
Severe AIDS ever (NHL/PML)	1.9	0.9–4.0	.07

NOTE. Laboratory markers were included as time-dependent categorical variables. CI, confidence interval; HAART, highly active antiretrovial therapy; HIV, human immunodeficiency virus; NHL, non-Hodgkin's lymphoma; PML, progressive multifocal leukoencephalopathy.

[a] Clinical status at the time of starting HAART was modeled as 3 categories: category 1, no current AIDS diagnosis (i.e., never had AIDS or an AIDS diagnosis other than PML or NHL) >12 months before starting HAART; category 2, had an AIDS diagnosis other than PML or NHL in past 12 months; category 3, ever been diagnosed with PML or NHL.

Table 3. Characteristics of 3 patient cohorts: derivation and validation cohorts.

Variables	EuroSIDA derivation cohort ($n = 2027$)	EuroSIDA validation cohort ($n = 1946$)	Barcelona validation cohort ($n = 1442$)
Demographic characteristics, no. (%) of patients			
Male	1548 (76)	1597 (82)	1032 (72)
Homosexual	880 (43)	1044 (54)	409 (30)
IDU	511 (25)	320 (16)	527 (38)
AIDS at start of HAART	450 (22)	683 (35)	222 (15)
CD4 cell count at HAART, median cells/mm^3 (IQR)	244 (134–357)	166 (70–294)[a]	221 (100–354)
Virus load at HAART, median HIV RNA copies/mL (IQR)	4.3 (3.5–4.9)	4.7 (4.0–5.3)[b]	4.61 (3.87–5.23)
Duration of follow-up, median months (IQR)	33 (20–41)	27 (13–42)	16 (10–18)
Age at HAART, median years (IQR)	37 (33–44)	37 (32–44)	32.0 (29.0–38.0)
Score at HAART, median (IQR)	2 (0–5)	2 (0–5)[c]	2 (0–5)
Clinical Events, no. (%)	200 (10)	183 (9)	77 (5)
PYFU	5173	4241	1682
Incidence (95% CI)	3.9 (3.4–4.4)	4.2 (3.6–4.8)	4.6 (4.0–5.2)

NOTE. "At HAART" is at the start of HAART (highly active antiretroviral therapy). CI, confidence interval; HIV, human immunodeficiency virus; IDU, injection drug user; IQR, interquartile range; PYFU, person-years of follow-up.

[a] $n = 1304$.

[b] $n = 1119$.

[c] $n = 955$.

calendar time, but there was no significant evidence for such a phenomenon. Similarly, there was no evidence that the predictive value of the score differed by duration of HAART. The predictive value of the score was also similar when we excluded from follow-up people whose CD4 cell count was <200 cells/mm^3 and for whom *P. carinii* prophylaxis was not being used.

Validation cohorts. In general, the characteristics of the 2 validation cohorts were similar to those of the derivation cohort (table 3). There was a higher proportion of injection drug users in the Barcelona validation cohort and a considerably lower median CD4 cell count at the start of HAART among patients from the EuroSIDA validation cohort. The median calendar date of initiation of HAART was December 1996 (IQR, August 1996–July 1997) for the EuroSIDA validation cohort and July 1997 (IQR, February 1997–April 1998) for the Barcelona validation cohort. The median score at the start of HAART was 2 in the EuroSIDA validation cohort (IQR, 0–5) and 2 in the Barcelona validation cohort (IQR, 0–5). The overall incidence of clinical progression was 3.9, 4.2, and 4.6 per 100 person-years for the EuroSIDA derivation cohort, EuroSIDA validation cohort, and the Barcelona validation cohort, respectively.

As shown in table 4, the 95% CIs around the incidence rates of clinical progression at specific scores within each cohort were wide, because of the limited follow-up in some cases. Although there was some variation between the cohorts in the incidence of clinical events, there was, in general, a high level of agreement and a similar pattern of increasing incidence of clinical events as the score increased. Estimates of the increased risk of clinical progression associated with a single point increase in the score from both Poisson regression and from Cox proportional hazards models show a good agreement between the derivation and both validation cohorts. In general, a single point increase in score was associated with an increased risk of clinical progression of ~40% (table 4).

Figure 1 shows the increasing incidence of clinical progression and increasing scores for all 3 cohorts combined. At a score of zero, the incidence rate of clinical progression was 1.0/100 PYFU (95% CI, 0.7–1.3/100 PYFU); this increased to 12.0/100 PYFU at a score of 6 (95% CI, 7.8–16.2/100 PYFU) and 142.9/100 PYFU at scores of $\geqslant 12$ (95% CI, 54.3–231.4/100 PYFU). We repeated the analysis of the incidence of clinical progression separately for AIDS-defining illnesses and deaths. In the combined 3 cohorts, there was comparable increase in the risk of either of those 2 end points for each unit increase in the score (42% [95% CI, 39%–46%] and 43% [95% CI, 37%–48%]), respectively, by Poisson regression. Furthermore, there were comparable increases in the risk of clinical progression associated with a 1 unit increase in the score between patients of white or other races, sex, PI or NNRTI HAART regimens, and between those who started HAART with a high or low score.

Discussion

We derived and independently validated a clinically prognostic scoring system for assessing the incidence of clinical disease progression among patients receiving HAART according to their current clinical status. The derived score was based on the latest information for 4 laboratory and clinical variables that were highly predictive of clinical progression. These were the only factors that independently predicted disease progression in

Table 4. Incidence of clinical progression: derivation and validation cohorts.

	EuroSIDA derivation cohort			EuroSIDA validation cohort			Barcelona validation cohort		
Score	Incidence	95% CI	Events/ person-years	Incidence	95% CI	Events/ person-years	Incidence	95% CI	Events/ person-years
0	1.4	0.9–2.0	26/1819	0.5	0.2–1.0	7/1437	0.8	0.3–2.0	5/589
1	1.6	0.7–2.9	10/623	1.5	0.5–3.2	6/405	1.5	0.3–4.4	3/200
2	1.8	1.0–2.5	19/1083	2.0	1.2–3.2	17/858	2.7	1.2–5.1	9/335
3	2.0	0.9–3.7	9/456	3.7	2.1–6.0	16/433	4.7	1.9–9.7	7/148
4	5.7	3.4–9.0	19/334	3.9	1.9–7.1	10/259	2.7	0.5–7.9	3/111
5	7.6	4.9–10.4	29/380	6.6	4.1–9.1	27/410	5.7	2.5–11.3	8/140
6	12.7	7.1–20.9	15/118	12.9	6.8–22.0	13/101	7.5	1.5–22.0	3/40
7	11.6	7.0–16.2	24/207	17.9	11.6–24.2	31/173	15.4	7.4–28.3	10/65
8	25.0	3.0–90.3	2/8	6.7	0.2–37.1	1/15	0.0	0.0–368.9	0/1
9	26.9	14.7–45.2	14/52	30.9	18.0–49.5	17/55	5.5	0.1–20.5	1/18
10	41.2	15.6–80.0	7/18	6.3	1.3–23.1	1/16	200.0	24.0–723.0	2/1
11	40.8	26.0–55.7	29/71	39.7	25.8–53.7	31/78	70.0	40.0–100.0	21/30
⩾12	66.7	8.0–240.0	2/3	300.0	110.0–655.0	6/2	100.0	12.0–360.0	2/2
RR/unit higher[a]	1.39	1.34–1.44		1.43	1.38–1.48			1.46	1.38–1.55
RH/higher[b]	1.38	1.33–1.43		1.41	1.36–1.46			1.43	1.35–1.52

NOTE. CI, confidence interval; RH, relative hazard; RR, rate ratio.

[a] Increased rate of clinical progression associated with single unit increase in score estimated from Poisson regression.

[b] Increased RH of clinical progression associated with single unit increase in score estimated by fitting score as time-updated covariate in a Cox proportional hazards model.

the derivation patient cohort. The predictive ability of the score was validated in 2 other cohorts with a high degree of precision; the relative risk of disease progression per 1 additional score point in the 3 cohorts was ~40%. This score is important because it provides the link between what can be regularly monitored and what is most clinically important—that is, the risk of overt clinical disease.

Our approach of using data that reflect a patient's current clinical status is most relevant to clinical practice. For a patient with a given score value, the incidence rate shown in figure 1 is the one that would be expected to apply over the ensuing ~3 months, the period over which clinic visits tend to be spaced. However, prediction over a longer period also would be useful. We found that the score does indeed discriminate among patients in regard to their risk of clinical disease for a 1-year period.

Many studies over the past 4 years have verified the independent prognostic role of absolute level and changes in virus load in response to antiretroviral therapy [10–15, 28–36], although a meta-analysis of 15 trials showed some variability in the consistency of this association [37]. In some studies, virus load was the strongest marker for prognosis [10, 32], whereas others suggested that virus load was a weak predictor in patients with advanced immunodeficiency [31, 35]. Many studies assessed patients receiving various nucleoside analogue therapies before the era of HAART and thus are not directly applicable to patients receiving HAART. Our data are not inconsistent with this body of evidence but emphasize that, in a setting in which laboratory marker values are updated as new measures are taken, the additional prognostic information provided by virus load is comparatively small after adjustment for other prognostic variables, such as CD4 cell count and hemoglobin level. Of note, most virus load measurements in EuroSIDA are determined by the Roche Amplicor system (64% of the sites uses this technique), but other less frequently used systems (e.g., the Chiron branched DNA system) may result in slightly lower readings of some specimens. If the latter system is used, clinicians should be aware that a person with a virus load of just below a cutoff point (i.e., 500 or 10,000 HIV RNA copies/mL) may have a value above the cutoff if the virus load were remeasured by the Roche assay. Such persons should be considered as potentially having a score 1 unit higher than that calculated by an assay that yields slightly lower results.

Of importance, our scoring system was not developed to assess the longer term prognosis of patients receiving HAART and thus should not be used as an argument against attempts to achieve optimal virus control. Complete virus control is indeed likely to be important to avoid the development of resistance [38, 39], which, in the longer term, probably limits the durability of response of the antiretroviral regimen that the patient is currently receiving. However, our results support the hypothesis that, as long as the CD4 cell count increases after the initiation of HAART, the patient is achieving some clinical benefit from therapy, even if the virus load is not totally suppressed [40, 41].

Previously, we [26] and others [42–44] reported the prognostic applications of the hemoglobin level. The grading of anemia used in the current analysis is similar to that described elsewhere by the EuroSIDA group [26]. The mechanism by which hemoglobin level is such a strong predictor of clinical prognosis remains to be determined. It is well known that the hemopoiesis of persons with severe infections is impaired. Therefore, patients with an ongoing illness that has not yet manifested itself as a AIDS-defining event (and thus is not counted as an end point in

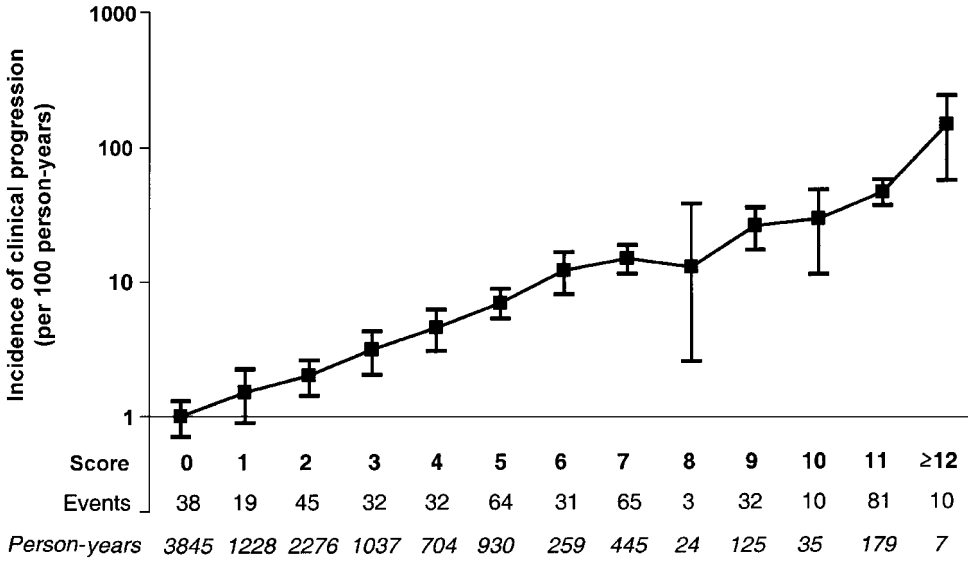

Figure 1. Incidence (95% confidence intervals) of clinical progression (new AIDS-defining event or death) for each value of the score in persons starting highly active antiretroviral therapy. Data are combined from 3 cohorts (see table 3; 5415 persons). Also shown are number of events and person-years of follow-up on which incidence estimates are based.

our analysis) may have a tendency to develop anemia. If so, anemia may act as a marker of ongoing, albeit undiagnosed, opportunistic disease. The reduction in size of the RHs with increasing lag time is consistent with this. Alternatively, anemia may be a marker of general immune activation that is associated with the progression of the HIV infection [45]. Any clinical benefit over and above symptomatic relief of the symptoms caused by the anemia, by correction of anemia by blood transfusion or other treatment (e.g., erythropoietin), should be examined in randomized controlled trials.

Several pre-HAART era studies identified the large variability in prognosis (even after adjustment for variations in level of immunodeficiency) for different AIDS-defining events [17, 25]. The 2 diseases with the poorest survival rate were consistently PML and NHL. Therefore, we considered these diagnoses separately from all other AIDS-defining illnesses. Of interest, the presence of either of these 2 illnesses resulted in an increased score, but no other AIDS-defining illnesses did so. In this way, the scoring of patients as they start HAART allows for recovery from a previous nonserious opportunistic infection without adding clinically prognostic information once HAART is initiated.

As would be expected, we found that the predictive ability of the score was substantially inferior if it was based only on variables available at the time of initiation of HAART (data not shown). We also investigated other potentially prognostic variables such as time receiving HAART (to assess whether the score remains clinically useful as time on HAART increases) or starting a new antiretroviral. After adjustment for changes in the CD4 cell count, level of anemia, and virus load, these potentially important variables were no longer independently predictive, although this should continue to be evaluated with more follow-up. The variables of CD4 cell count, hemoglobin level, and clinical status were also highly predictive of clinical disease progression before the introduction of HAART. There were insufficient data on virus load from this time period for comment. It should also be noted that some patients interrupt HAART for a period of time. We could not evaluate whether the clinical risk associated with a given score value remained the same in people who were not receiving therapy. In the absence of such evidence, it seems most prudent to assume that the clinical risk estimates that we have provided apply only to those continuing to receive HAART.

Our scoring system is, as are most others, a simplification of the information on which it is based. The score was intentionally constructed in a way that makes it easy to remember and implement in clinical practice. Ultimately, assessing the laboratory markers as continuous log-transformed variables provided the best predictor of clinical progression but would be difficult to use. Some arbitrary cutoffs of the laboratory markers were therefore needed. These were decided before the initiation of this analysis, on the basis of previously reported studies and commonly used cutoffs. However, such a simplification can be criticized. For example, a patient with several CD4 cell counts in the range of 55–90 cells/mm^3 over the past year now has a cell count of 49 cells/mm^3, which adds 4 score points to his overall score. This may be an indicator of disease progression, particularly if subsequent measurements are consistent, but it may also be due to assay variations. Updating the score with the next available laboratory data will help to confirm whether the patient was at an increased risk of clinical progression. Furthermore, a patient with, for example, a CD4 cell count of 49 cells/mm^3 does not carry exactly the same risk as a person with a CD4 cell

count of <5 cells/mm^3. Clearly, clinical judgment should be used in the interpretation of the results from the score, together with information from repeated laboratory tests.

There are several other important limitations in the use of this scoring system. All patients included in the study had started HAART but not agents that specifically stimulate the immune system (e.g., interleukin [IL]–2) [46]. It remains to be demonstrated whether the "quality" of the CD4 cells produced in peripheral blood with IL-2 are of equal clinical efficacy with those produced in conjunction with HAART. Other factors, such as duration of HAART therapy (assessed but not found to be of importance) or comorbidities (e.g., hepatitis), may influence the long-term prognosis of patients on HAART, possibly through inducing late-onset fatal adverse events. The predictability of the score should be reevaluated as more experience with HAART accumulates. Also, our score was based mainly on the use of PIs, rather than NNRTIs, in the HAART regimen. We found no significant evidence for differences in the incidence of clinical disease for different score values for patients taking NNRTI-based HAART regimens, but this remains a possibility. Furthermore, the results should be extrapolated with caution to areas of the world where the HIV-related disease pattern and causes of death differ from those observed here. For example, persons who start HAART in Southeast Asia and Africa may be at substantially higher risk of specific AIDS-defining illnesses, such as tuberculosis. Thus, other prognostic variables may be more important in those areas, and there may be population-based differences in hemoglobin levels. Finally, most patients included in our analysis received appropriate disease-specific prophylaxis based on current guidelines [47] (e.g., 85% of patients with CD4 cell counts <200 cells/mm^3 had prophylaxis to prevent the development of *P. carinii* pneumonia), and, hence, application of the score on other populations assumes that these guidelines are followed.

There are several situations in which this scoring system could be used. On a population basis, the score would characterize the health status of a group of patients on HAART for use in comparison with other cohorts and would assess changes in the risk of clinical progression over time. For individual patients receiving HAART under routine care, the score could be used to identify patients who are at highest risk of clinical disease progression.

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